

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>C07D 413/12, A61K 31/42, C07D 263/58, 417/12, 235/30</b>		A1	(11) International Publication Number: <b>WO 98/40381</b>
			(43) International Publication Date: 17 September 1998 (17.09.98)
(21) International Application Number: PCT/US98/04932		Simpson Road, Marlborough, MA 01752 (US). NAEGELE, Doug [US/US]; Apartment 2, 61 Bay State Avenue, Somerville, MA 02144 (US). NOVAK, Perry, M. [US/US]; 35 Debbie Lane, Milford, MA 01757 (US). PEARLMAN, David, A. [US/US]; 150 Jason Street, Arlington, MA 02174 (US). RONKIN, Steven, M. [US/US]; 39 Bridge Street #14, Watertown, MA 02172 (US).  (74) Agents: HALEY, James, F., Jr.; Fish & Neave, 1251 Avenue of the Americas, New York, NY 10020 (US) et al.  (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 13 March 1998 (13.03.98)			
(30) Priority Data: 08/816,764 14 March 1997 (14.03.97) US 60/042,443 28 March 1997 (28.03.97) US			
(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 08/816,764 (CIP) Filed on 14 March 1997 (14.03.97)			
(71) Applicant (for all designated States except US): VERTEX PHARMACEUTICALS INCORPORATED [US/US]; 130 Waverly Street, Cambridge, MA 02139-4242 (US).			
(72) Inventors; and (75) Inventors/Applicants (for US only): SAUNDERS, Jeffrey, O. [US/US]; 164 Parker Street, Acton, MA 01720 (US). ARMISTEAD, David, M. [US/US]; Five Cutting Drive, Maynard, MA 01574 (US). BADIA, Michael, C. [US/US]; 20 Meadowbrook Road, Bedford, MA 01730 (US). BETHIEL, Randy, S. [US/US]; 28 Haskell Street, Allston, MA 02134 (US). FRANK, Catharine, A. [US/US]; 374			

## Published

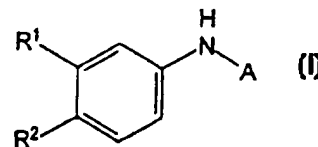
With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: INHIBITORS OF IMPDH ENZYME

## (57) Abstract

The present invention relates to a novel class of compounds of formula (I) which are IMPDH inhibitors. This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting IMPDH enzyme activity and consequently may be advantageously used as therapeutic agents for IMPDH mediated processes. This invention also relates to methods for inhibiting the activity of IMPDH using the compounds of formula (I) and related compounds, wherein A is a saturated, unsaturated or partially saturated monocyclic or bicyclic ring system optionally comprising up to 4 heteroatoms selected from N, O, and S wherein each A optionally comprises up to 4 substituents selected from R<sup>1</sup>, R<sup>4</sup> and R<sup>5</sup>; each R<sup>1</sup> is halogen, CN, NO<sub>2</sub>, CF<sub>3</sub>, OCF<sub>3</sub>, OH, R<sup>3</sup>, OR<sup>3</sup>, 1,2-methylenedioxy, 1,2-ethylenedioxy, SR<sup>3</sup>, S(O)R<sup>3</sup>, SO<sub>2</sub>R<sup>3</sup>, NH<sub>2</sub>, NHR<sup>3</sup>, N(R<sup>3</sup>)<sub>2</sub>, NR<sup>3</sup>R<sup>9</sup>, COOH, or COOR<sup>3</sup>; each R<sup>2</sup> is independently R<sup>1</sup> or a monocyclic ring system consisting of 5 to 6 members per ring, wherein said ring system optionally comprises up to 4 heteroatoms selected from N, O, and S, and wherein a CH<sub>2</sub> adjacent to said N, O or S may be substituted with C(O); and each R<sup>2</sup> optionally comprises up to 2 substituents, each substituent independently selected from R<sup>1</sup>.



**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Turkmenistan
BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

## INHIBITORS OF IMPDH ENZYME

### TECHNICAL FIELD OF THE INVENTION

5           The present invention relates to a novel  
class of compounds which inhibit IMPDH. This invention  
also relates to pharmaceutical compositions comprising  
these compounds. The compounds and pharmaceutical  
compositions of this invention are particularly well  
10 suited for inhibiting IMPDH enzyme activity and  
consequently, may be advantageously used as therapeutic  
agents for IMPDH mediated processes. This invention  
also relates to methods for inhibiting the activity of  
IMPDH using the compounds of this invention and related  
15 compounds.

### BACKGROUND OF THE INVENTION

The synthesis of nucleotides in organisms is  
required for the cells in those organisms to divide and  
replicate. Nucleotide synthesis in mammals may be  
achieved through one of two pathways: the *de novo*  
synthesis pathway or the salvage pathway. Different  
cell types use these pathways to a different extent.

- 2 -

Inosine-5'-monophosphate dehydrogenase (IMPDH; EC 1.1.1.205) is an enzyme involved in the *de novo* synthesis of guanosine nucleotides. IMPDH catalyzes the NAD-dependent oxidation of inosine-5'-monophosphate (IMP) to xanthosine-5'-monophosphate (XMP) [Jackson R.C. et. al., Nature, 256, pp. 331-333, (1975)].

IMPDH is ubiquitous in eukaryotes, bacteria and protozoa [Y. Natsumeda & S.F. Carr, Ann. N.Y. Acad., 696, pp. 88-93 (1993)]. The prokaryotic forms share 30-40% sequence identity with the human enzyme. Regardless of species, the enzyme follows an ordered Bi-Bi reaction sequence of substrate and cofactor binding and product release. First, IMP binds to IMPDH. This is followed by the binding of the cofactor NAD. The reduced cofactor, NADH, is then released from the complex, followed by the product, XMP [S.F. Carr et al., J. Biol. Chem., 268, pp. 27286-90 (1993); E.W. Holmes et al., Biochim. Biophys. Acta, 364, pp. 209-217 (1974)]. This mechanism differs from that of most other known NAD-dependent dehydrogenases, which have either a random order of substrate addition or require NAD to bind before the substrate.

Two isoforms of human IMPDH, designated type I and type II, have been identified and sequenced [F.R. Collart and E. Huberman, J. Biol. Chem., 263, pp. 15769-15772, (1988); Y. Natsumeda et. al., J. Biol. Chem., 265, pp. 5292-5295, (1990)]. Each is 514 amino acids, and they share 84% sequence identity. Both IMPDH type I and type II form active tetramers in solution, with subunit molecular weights of 56 kDa [Y. Yamada et. al., Biochemistry, 27, pp. 2737-2745 (1988)].

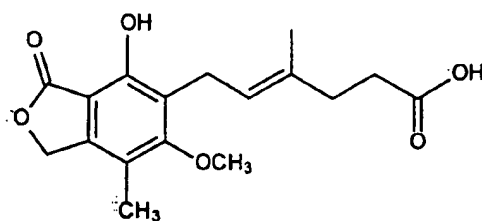
- 3 -

The *de novo* synthesis of guanosine nucleotides, and thus the activity of IMPDH, is particularly important in B and T-lymphocytes. These cells depend on the *de novo*, rather than salvage  
5 pathway to generate sufficient levels of nucleotides necessary to initiate a proliferative response to mitogen or antigen [A.C. Allison et. al., Lancet II, 1179, (1975) and A.C. Allison et. al., Ciba Found. Symp., 48, 207, (1977)]. Thus, IMPDH is an attractive  
10 target for selectively inhibiting the immune system without also inhibiting the proliferation of other cells.

Immunosuppression has been achieved by inhibiting a variety of enzymes including for example,  
15 the phosphatase calcineurin (inhibited by cyclosporin and FK-506); dihydroorotate dehydrogenase, an enzyme involved in the biosynthesis of pyrimidines (inhibited by leflunomide and brequinar); the kinase FRAP (inhibited by rapamycin); and the heat shock protein  
20 hsp70 (inhibited by deoxyspergualin). [See B. D. Kahan, Immunological Reviews, 136, pp. 29-49 (1993); R. E. Morris, The Journal of Heart and Lung Transplantation, 12(6), pp. S275-S286 (1993)].

Inhibitors of IMPDH are also known. United  
25 States patents 5,380,879 and 5,444,072 and PCT publications WO 94/01105 and WO 94/12184 describe mycophenolic acid (MPA) and some of its derivatives as potent, uncompetitive, reversible inhibitors of human IMPDH type I ( $K_i=33$  nM) and type II ( $K_i=9$  nM). MPA has  
30 been demonstrated to block the response of B and T-cells to mitogen or antigen [A. C. Allison et. al., Ann. N. Y. Acad. Sci., 696, 63, (1993)].

- 4 -

**MPA**

Immunosuppressants, such as MPA, are useful drugs in the treatment of transplant rejection and autoimmune diseases. [R. E. Morris, Kidney Intl., 49, 5 Suppl. 53, S-26, (1996)]. However, MPA is characterized by undesirable pharmacological properties, such as gastrointestinal toxicity and poor bioavailability. [L. M. Shaw, et. al., Therapeutic Drug 10 Monitoring, 17, pp. 690-699, (1995)].

Nucleoside analogs such as tiazofurin, ribavirin and mizoribine also inhibit IMPDH [L. Hedstrom, et. al. Biochemistry, 29, pp. 849-854 (1990)]. These compounds, which are competitive 15 inhibitors of IMPDH, suffer from lack of specificity to this enzyme.

Mycophenolate mofetil, a prodrug which quickly liberates free MPA *in vivo*, was recently approved to prevent acute renal allograft rejection 20 following kidney transplantation. [L. M. Shaw, et. al., Therapeutic Drug Monitoring, 17, pp. 690-699, (1995); H. W. Sollinger, Transplantation, 60, pp. 225-232 (1995)]. Several clinical observations, however, limit the therapeutic potential of this drug. [L. M. 25 Shaw, et. al., Therapeutic Drug Monitoring, 17, pp. 690-699, (1995)]. MPA is rapidly metabolized to the inactive glucuronide *in vivo*. [A.C., Allison and E.M. Eugui, Immunological Reviews, 136, pp. 5-28 (1993)].

- 5 -

The glucuronide then undergoes enterohepatic recycling causing accumulation of MPA in the gastrointestinal tract where it cannot exert its IMPDH inhibitory activity on the immune system. This effectively lowers the drug's *in vivo* potency, while increasing its undesirable gastrointestinal side effects.

It is also known that IMPDH plays a role in other metabolic events. Increased IMPDH activity has been observed in rapidly proliferating human leukemic cell lines and other tumor cell lines, indicating IMPDH as a target for anticancer as well as immunosuppressive chemotherapy [M. Nagai et. al., Cancer Res., 51, pp. 3886-3890, (1991)]. IMPDH has also been shown to play a role in the proliferation of smooth muscle cells, indicating that inhibitors of IMPDH, such as MPA or rapamycin, may be useful in preventing restenosis or other hyperproliferative vascular diseases [C. R. Gregory et al., Transplantation, 59, pp. 655-61 (1995); PCT publication WO 94/12184; and PCT publication WO 94/01105].

Additionally, IMPDH has been shown to play a role in viral replication in some viral cell lines. [S.F. Carr, J. Biol. Chem., 268, pp. 27286-27290 (1993)]. Analogous to lymphocyte and tumor cell lines, the implication is that the *de novo*, rather than the salvage, pathway is critical in the process of viral replication.

The IMPDH inhibitor ribavirin is currently being evaluated for the treatment of hepatitis C virus (HCV) and hepatitis B virus (HBV) infection and disease. Ribavirin enhances the sustained efficacy of interferon in HBV and HCV treatment. However, the therapeutic potential of ribavirin is limited by its

- 6 -

lack of a sustained response in monotherapy and broad cellular toxicity.

Thus, there remains a need for potent IMPDH inhibitors with improved pharmacological properties.

- 5 Such inhibitors would have therapeutic potential as immunosuppressants, anticancer agents, antivascular hyperproliferative agents, antiinflammatory agents, antifungal agents, antipsoriatic and antiviral agents.

10 SUMMARY OF THE INVENTION

The present invention provides compounds, and pharmaceutically acceptable derivatives thereof, that are useful as inhibitors of IMPDH. These compounds can be used alone or in combination with other therapeutic  
15 or prophylactic agents, such as antivirals, antiinflammatory agents, antibiotics, and immunosuppressants for the treatment or prophylaxis of transplant rejection and autoimmune disease. Additionally, these compounds are useful, alone or in  
20 combination with other agents, as therapeutic and prophylactic agents for antiviral, antitumor, anticancer, antiinflammatory, antifungal, antipsoriatic, immunosuppressive, and restenosis therapy regimens.

- 25 The invention also provides pharmaceutical compositions comprising the compounds of this invention, as well as multi-component compositions comprising additional IMPDH compounds together with an immunosuppressant. The invention also provides methods  
30 of using the compounds of this invention, as well as other related compounds, for the inhibition of IMPDH.

The compounds of this invention, as well as those used in the methods of this invention demonstrate



- 7 -

a different metabolic profile than MPA and its derivatives. Because of this difference, methods of this invention and the compounds used therein may offer advantages as therapeutics for IMPDH mediated disease.

- 5 These advantages include increased overall therapeutic benefit and reduction in deleterious side effects.

#### DETAILED DESCRIPTION OF THE INVENTION

In order that the invention herein described  
10 may be more fully understood, the following detailed description is set forth. In the description, the following abbreviations are used:

	<u>Designation</u>	<u>Reagent or Fragment</u>
15	Ac	acetyl
	Me	methyl
	Et	ethyl
	Bn	benzyl
	CDI	carbonyldiimidazole
20	DIEA	diisopropylethylamine
	DMAP	dimethylaminopyridine
	DMF	dimethylformamide
	DMSO	dimethylsulfoxide
	EDC	1-(3-dimethylaminopropyl)-3-
25		ethylcarbodiimide hydrochloride
	EtOAc	ethyl acetate
	THF	tetrahydrofuran

The following terms are employed herein:

- 8 -

Unless expressly stated to the contrary, the terms  $-SO_2-$  and  $-S(O)_2-$  as used herein refer to a sulfone or sulfone derivative (i.e., both appended groups linked to the S), and not a sulfinic ester.

5           The terms halo or halogen refer to a radical of fluorine, chlorine, bromine or iodine.

          The term immunosuppressant refers to a compound or drug which possesses immune response inhibitory activity. Examples of such agents include  
10 cyclosporin A, FK506, rapamycin, leflunomide, deoxyspergualin, prednisone, azathioprine, mycophenolate mofetil, OKT3, ATAG, interferon and mizoribine.

          The term interferon refers to all forms of  
15 interferons, including but not limited to alpha, beta and gamma forms.

          IMPDH-mediated disease refers to any disease state in which the IMPDH enzyme plays a regulatory role in the metabolic pathway of that disease. Examples of  
20 IMPDH-mediated disease include transplant rejection and autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis, juvenile diabetes, asthma, and inflammatory bowel disease, as well as inflammatory diseases, cancer, viral replication diseases, and  
25 vascular diseases.

          For example, the compounds, compositions and methods of using them of this invention may be used in the treatment of transplant rejection (e.g., kidney, liver, heart, lung, pancreas (islet cells), bone  
30 marrow, cornea, small bowel and skin allografts and

- 9 -

heart valve xenografts) and autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis, juvenile diabetes, asthma, inflammatory bowel disease (Crohn's disease, ulcerative colitis), lupus, diabetes, mellitus

5 myasthenia gravis, psoriasis, dermatitis, eczema, seborrhea, pulmonary inflammation, eye uveitis, hepatitis, Grave's disease, Hashimoto's thyroiditis, Behcet's or Sjorgen's syndrome (dry eyes/mouth), pernicious or immunohaemolytic anaemia, idiopathic

10 adrenal insufficiency, polyglandular autoimmune syndrome, and glomerulonephritis, scleroderma, lichen planus, viteligo (depigmentation of the skin), autoimmune thyroiditis, and alveolitis, inflammatory diseases such as osteoarthritis, acute pancreatitis,

15 chronic pancreatitis, asthma and adult respiratory distress syndrome, as well as in the treatment of cancer and tumors, such as solid tumors, lymphomas and leukemia, vascular diseases, such as restenosis, stenosis and arteriosclerosis, and viral DNA and RNA

20 replication diseases.

Additionally, IMPDH enzymes are also known to be present in bacteria and thus may regulate bacterial growth. As such, the IMPDH-inhibitor compounds, compositions and methods described herein

25 may be useful in treatment or prevention of bacterial infection, alone or in combination with other antibiotic agents.

The term "treating" as used herein refers to the alleviation of symptoms of a particular disorder in

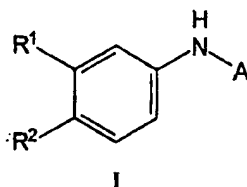
30 a patient or the improvement of an ascertainable measurement associated with a particular disorder. As

- 10 -

used herein, the term "patient" refers to a mammal, including a human.

The terms "HBV", "HCV" and "HGV" refer to hepatitis-B, hepatitis-C and hepatitis-G virus, respectively.

According to one embodiment, the invention provides methods of inhibiting IMPDH activity in a mammal comprising the step of administering to said mammal, a compound of formula I:



10 wherein:

A is a saturated, unsaturated or partially saturated monocyclic or bicyclic ring system optionally comprising up to 4 heteroatoms selected from N, O, and S wherein each A optionally comprises up to 4 substituents selected from R<sup>1</sup>, R<sup>4</sup> and R<sup>5</sup>;

each R is halogen, CN, NO<sub>2</sub>, CF<sub>3</sub>, OCF<sub>3</sub>, OH, R<sup>3</sup>, OR<sup>3</sup>, 1,2-methylenedioxy, 1,2-ethylenedioxy, SR<sup>3</sup>, S(O)R<sup>3</sup>, SO<sub>2</sub>R<sup>3</sup>, NH<sub>2</sub>, NHR<sup>3</sup>, N(R<sup>3</sup>)<sub>2</sub>, NR<sup>3</sup>R<sup>9</sup>, COOH, or COOR<sup>3</sup>;

each R<sup>2</sup> is independently R<sup>1</sup> or a monocyclic ring system consisting of 5 to 6 members per ring, wherein said ring system optionally comprises up to 4 heteroatoms selected from N, O, and S, and wherein a CH<sub>2</sub> adjacent to said N, O or S maybe substituted with C(O); and each R<sup>2</sup> optionally comprises up to 2

- 11 -

substituents, each substituent independently selected from R<sup>1</sup>;

each R<sup>3</sup> is independently (C<sub>1</sub>-C<sub>4</sub>)-straight or branched alkyl, or (C<sub>2</sub>-C<sub>4</sub>)-straight or branched alkenyl  
 5 or alkynyl;

each R<sup>4</sup> is independently (C<sub>1</sub>-C<sub>6</sub>)-straight or branched alkyl, or (C<sub>2</sub>-C<sub>6</sub>)-straight or branched alkenyl or alkynyl; and each R<sup>4</sup> optionally comprises up to 2 substituents, wherein:

10 the first of said substituents, if present, is R<sup>1</sup>, R<sup>5</sup> or R<sup>8</sup>, and  
 the second of said substituents, if present, is R<sup>1</sup>;

each R<sup>5</sup> is independently selected from OR<sup>6</sup>,  
 15 OC(O)R<sup>7</sup>, OC(O)R<sup>6</sup>, OC(O)OR<sup>7</sup>, OC(O)OR<sup>6</sup>, OC(O)N(R<sup>7</sup>)<sub>2</sub>,  
 OP(O)(OR<sup>7</sup>)<sub>2</sub>, SR<sup>7</sup>, SR<sup>6</sup>, S(O)R<sup>7</sup>, S(O)R<sup>6</sup>, SO<sub>2</sub>R<sup>7</sup>, SO<sub>2</sub>R<sup>6</sup>,  
 SO<sub>2</sub>N(R<sup>7</sup>)<sub>2</sub>, SO<sub>2</sub>NR<sup>6</sup>R<sup>7</sup>, SO<sub>3</sub>R<sup>7</sup>, C(O)R<sup>6</sup>, C(O)OR<sup>6</sup>, C(O)R<sup>7</sup>,  
 C(O)OR<sup>7</sup>, NC(O)C(O)R<sup>7</sup>, NC(O)C(O)R<sup>6</sup>, NC(O)C(O)OR<sup>7</sup>,  
 NC(O)C(O)N(R<sup>7</sup>)<sub>2</sub>, C(O)N(R<sup>7</sup>)<sub>2</sub>, C(O)N(OR<sup>7</sup>)R<sup>7</sup>,  
 20 C(O)N(OR<sup>7</sup>)R<sup>6</sup>, C(NOR<sup>7</sup>)R<sup>7</sup>, C(NOR<sup>7</sup>)R<sup>6</sup>, N(R<sup>7</sup>)<sub>2</sub>, NR<sup>7</sup>C(O)R<sup>6</sup>,  
 NR<sup>7</sup>C(O)R<sup>7</sup>, NR<sup>6</sup>C(O)R<sup>6</sup>, NR<sup>7</sup>C(O)OR<sup>7</sup>, NR<sup>7</sup>C(O)OR<sup>6</sup>,  
 NR<sup>7</sup>C(O)N(R<sup>7</sup>)<sub>2</sub>, NR<sup>7</sup>C(O)NR<sup>6</sup>R<sup>7</sup>, NR<sup>7</sup>SO<sub>2</sub>R<sup>7</sup>, NR<sup>7</sup>SO<sub>2</sub>R<sup>6</sup>,  
 NR<sup>7</sup>SO<sub>2</sub>N(R<sup>7</sup>)<sub>2</sub>, NR<sup>7</sup>SO<sub>2</sub>NR<sup>6</sup>R<sup>7</sup>, N(OR<sup>7</sup>)R<sup>7</sup>, N(OR<sup>7</sup>)R<sup>6</sup>,  
 P(O)(OR<sup>7</sup>)N(R<sup>7</sup>)<sub>2</sub>, P(O)(OR<sup>7</sup>)<sub>2</sub>, P(O)(N(R<sup>7</sup>)<sub>2</sub>)<sub>2</sub>, and  
 25 P(O)(OR<sup>7</sup>)R<sup>7</sup>.

- 12 -

$R^6$  is a monocyclic or a bicyclic ring system consisting of 5 to 6 members per ring, wherein said ring system optionally comprises up to 4 heteroatoms selected from N, O, and S, and wherein a  $CH_2$  adjacent to any of said N, O, or S heteroatoms is optionally substituted with C(O); and each  $R^6$  optionally comprises up to 3 substituents, each substituent independently selected from  $R^1$ ;

each  $R^7$  is independently H,  $(C_1-C_4)$ -straight or branched alkyl, or  $(C_2-C_4)$  straight or branched alkenyl; and each  $R^7$  optionally comprises a substituent that is  $R^8$ ;

$R^8$  is a monocyclic or a bicyclic ring system consisting of 5 to 6 members per ring, wherein said ring system optionally comprises up to 4 heteroatoms selected from N, O, and S, and wherein a  $CH_2$  adjacent to said N, O or S maybe substituted with C(O); and each  $R^8$  optionally comprises up to 2 substituents independently chosen from H,  $(C_1-C_4)$ -straight or branched alkyl,  $(C_2-C_4)$  straight or branched alkenyl, 1,2-methylenedioxy, 1,2-ethylenedioxy and  $(CH_2)_n-R^1$ ;

wherein n is 0, 1 or 2;

$R^9$  is an amino protecting group; and

wherein any carbon atom in any  $R^3$ ,  $R^4$  or  $R^7$  is optionally replaced by O, S, SO,  $SO_2$ , NH, or  $N(C_1-C_4)$ -alkyl.

- 13 -

The term "substituted" refers to the replacement of one or more hydrogen radicals in a given structure with a radical selected from a specified group. When more than one hydrogen radical may be replaced with a substituent selected from the same specified group, the substituents may be either the same or different at every position.

The term "monocyclic or bicyclic ring system consisting of 5 to 6 members per ring" refers to 5 or 6 member monocyclic rings and 8, 9 and 10 membered bicyclic ring structures, wherein each bond in each ring may possess any degree of saturation that is chemically feasible. When such structures contain substituents, those substituents may be at any position of the ring system, unless otherwise specified.

As specified, such ring systems may optionally comprise up to 4 heteroatoms selected from N, O or S. Those heteroatoms may replace any carbon atoms in these ring systems as long as the resulting compound is chemically stable.

The term "amino protecting group" refers to a suitable chemical group which may be attached to a nitrogen atom. The term "protected" refers to when the designated functional group is attached to a suitable chemical group (protecting group). Examples of suitable amino protecting groups and protecting groups are described in T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); L. Paquette, ed. Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons

- 14 -

(1995) and are exemplified in certain of the specific compounds used in this invention.

Preferably, in methods employing the compounds of formula I, each A optionally comprises up to 4 substituents selected from  $R^1$ ,  $R^4$  and  $R^5$ , preferably wherein at least one substituent, if present, is selected from  $R^4$  and  $R^5$ ; also preferably wherein A comprises up to 4 substituents, each independently selected from  $R^1$ ; and also preferably wherein A comprises up to 4 substituents, one substituent, if present, is selected from  $R^4$  and  $R^5$  and the remaining substituents, if present, are independently selected from  $R^1$ .

More preferably, in methods employing the compounds of formula I, A is a monocyclic aromatic ring system optionally comprising up to 4 heteroatom selected from N, O, and S wherein each A optionally comprises up to 4 substituents selected from  $R^1$ ,  $R^4$  and  $R^5$ , preferably wherein at least one substituent, if present, is selected from  $R^4$  and  $R^5$ ; also preferably wherein A comprises up to 4 substituents, each independently selected from  $R^1$ ; and also preferably wherein A comprises up to 4 substituents, one substituent, if present, is selected from  $R^4$  and  $R^5$  and the remaining substituents, if present, are independently selected from  $R^1$ .

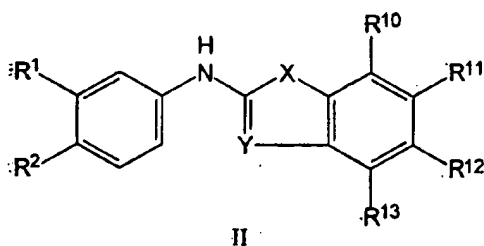
Also more preferably, in methods employing the compounds of formula I, A is a bicyclic aromatic



- 15 -

ring system optionally comprising up to 4 heteroatoms selected from N, O, and S, wherein each A optionally comprises up to 4 substituents selected from R<sup>1</sup>, R<sup>4</sup> and R<sup>5</sup>, preferably wherein at least one substituent, if present, is selected from R<sup>4</sup> and R<sup>5</sup>; also preferably wherein A comprises up to 4 substituents, each independently selected from R<sup>1</sup>; and also preferably wherein A comprises up to 4 substituents, one substituent, if present, is selected from R<sup>4</sup> and R<sup>5</sup> and the remaining substituents, if present, are independently selected from R<sup>1</sup>.

More preferably, in methods employing the compounds of formula I, are those methods wherein the compound has the structure of the formula:



15

wherein:

R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup> and R<sup>13</sup> are each independently selected from R<sup>1</sup> and R<sup>4</sup>, wherein only one of R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup> and R<sup>13</sup> may simultaneously be R<sup>4</sup>; and

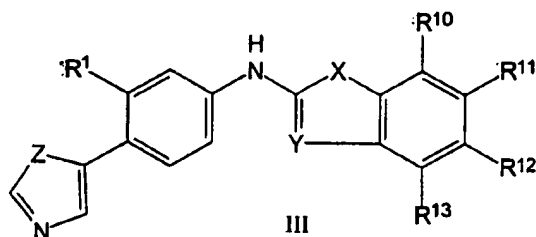
X and Y are independently selected from CH<sub>2</sub>, CHR<sup>3</sup>, CHR<sup>4</sup>, O, S, NH, NR<sup>3</sup>, NR<sup>4</sup>, CH, CR<sup>3</sup>, CR<sup>4</sup>, and N.

The present invention also provides compounds which are useful in inhibiting IMPDH. According to one

- 16 -

embodiment, the compounds have the structure and definitions of formula I above. Preferably, the invention provides compounds with the structure and definitions of formula II above.

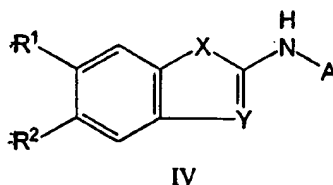
5 More preferably, the invention provides a compound of formula III:



10 wherein

$R^1$ ,  $R^{10}$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{13}$ , X and Y are as defined in formula II and Z is O, S, NH or  $NR^3$ , wherein  $R^3$  is as defined in formula I.

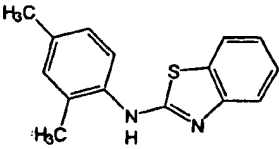
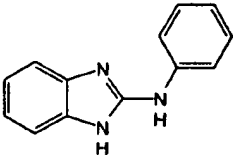
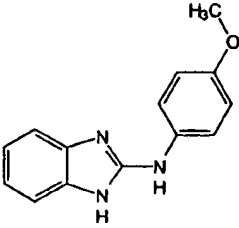
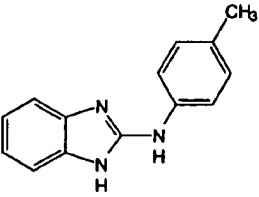
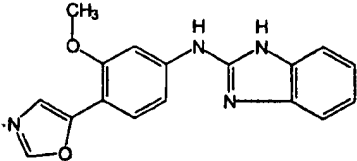
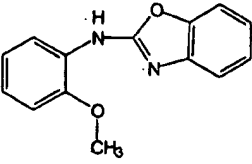
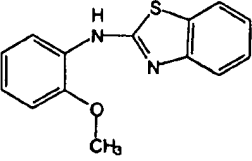
According to an alternate embodiment, the  
15 invention provides a compound of the formula IV:

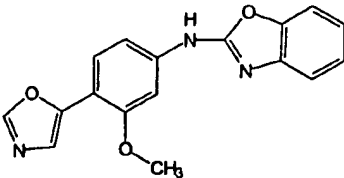
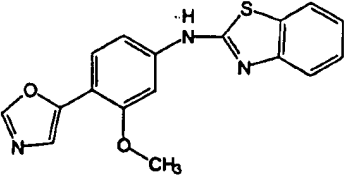
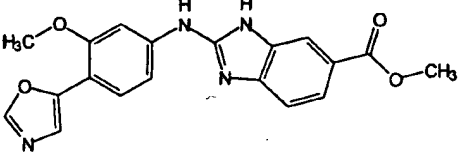
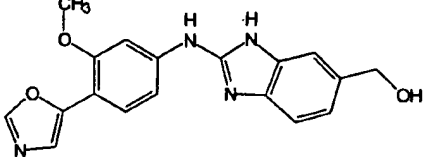
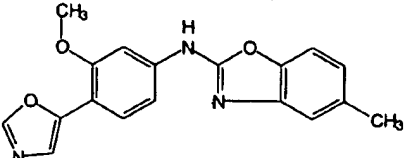
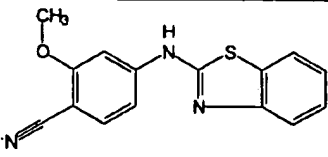
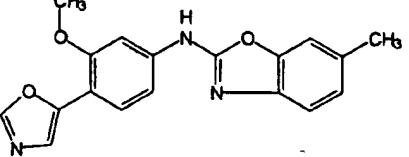
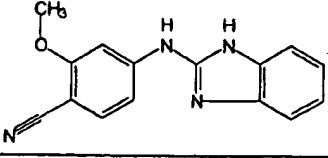


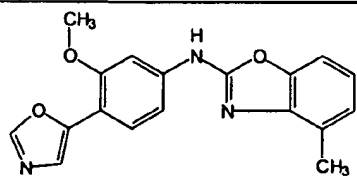
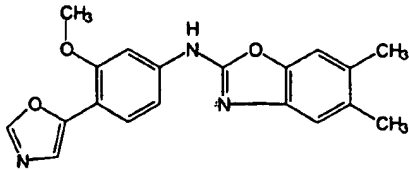
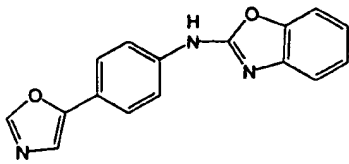
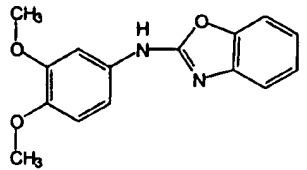
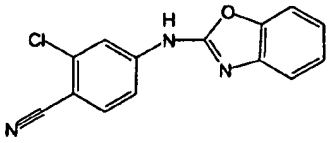
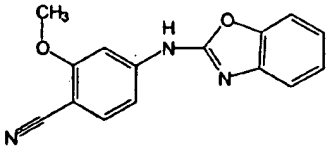
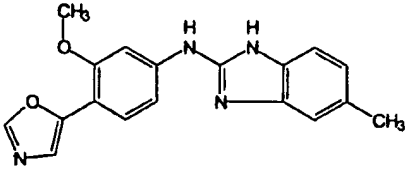
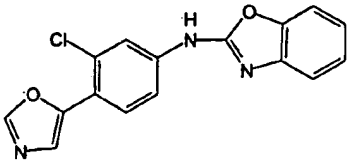
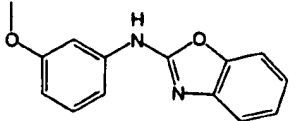
wherein  $R^1$ ,  $R^2$ , A, X and Y are as defined for formula II.

Table I lists preferred individual compounds  
20 of the invention and preferred compounds employed in the compositions and methods of this invention.

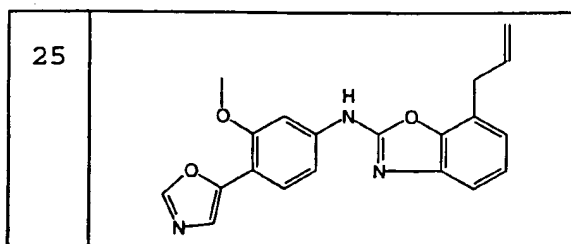
Table I

1	
2	
3	
4	
5	
6	
7	

8	
9	
10	
11	
12	
13	
14	
15	

16	
17	
18	
19	
20	
21	
22	
23	
24	

- 20 -



The compounds of this invention may contain  
5 one or more asymmetric carbon atoms and thus may occur  
as racemates and racemic mixtures, single enantiomers,  
diastereomeric mixtures and individual diastereomers.  
All such isomeric forms of these compounds are  
expressly included in the present invention. Each  
10 stereogenic carbon may be of the R or S configuration.

Combinations of substituents and variables  
envisioned by this invention are only those that result  
in the formation of stable compounds. The term  
"stable", as used herein, refers to compounds which  
15 possess stability sufficient to allow manufacture and  
which maintains the integrity of the compound for a  
sufficient period of time to be useful for the purposes  
detailed herein (e.g., therapeutic or prophylactic  
administration to a mammal or for use in affinity  
20 chromatography applications). Typically, such  
compounds are stable at a temperature of 40 °C or less,  
in the absence of moisture or other chemically reactive  
conditions, for at least a week.

As used herein, the compounds of this  
25 invention, including the compounds of formulae I-IV,  
are defined to include pharmaceutically acceptable

- 21 -

derivatives or prodrugs thereof. A "pharmaceutically acceptable derivative or prodrug" means any pharmaceutically acceptable salt, ester, salt of an ester, or other derivative of a compound of this invention which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound of this invention. Particularly favored derivatives and prodrugs are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a mammal (e.g., by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a biological compartment (e.g., the brain or lymphatic system) relative to the parent species. Preferred prodrugs include derivatives where a group which enhances aqueous solubility or active transport through the gut membrane is appended to the structure of formulae I-IV.

Pharmaceutically acceptable salts of the compounds of this invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acid salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, malonate, methanesulfonate, 2-

- 22 -

naphthalenesulfonate, nicotinate, nitrate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, thiocyanate, tosylate and  
5 undecanoate. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

10 Salts derived from appropriate bases include alkali metal (e.g., sodium, potassium), alkaline earth metal (e.g., magnesium), ammonium and N-(C<sub>1-4</sub> alkyl)<sub>4</sub><sup>+</sup> salts.

This invention also envisions the  
15 quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersible products may be obtained by such quaternization.

The compounds of this invention may be  
20 synthesized using conventional techniques. Advantageously, these compounds are conveniently synthesized from readily available starting materials.

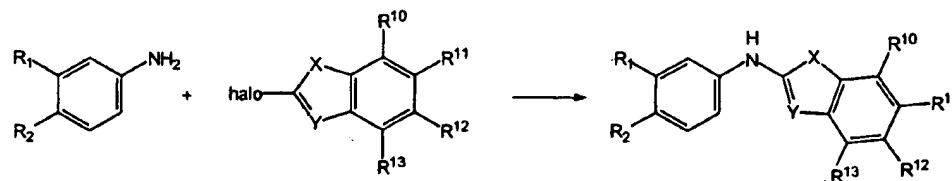
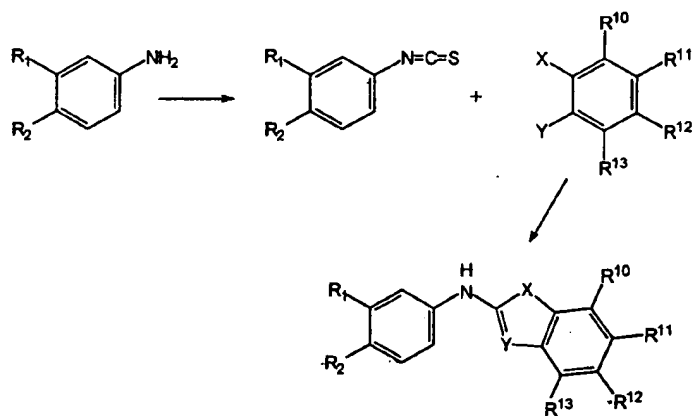
In general, compounds of formula I-IV are conveniently obtained via methods illustrated in  
25 General Synthetic Schemes 1-2.

In General Synthetic Scheme 1 (see below), an A, B, C, D-substituted aniline is reacted with an R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup>-substituted halo-substituted heterocycle under standard conditions to give the desired amine.



- 23 -

In this process, A, B, C, D and R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup> may be one or more independent substituents (or their suitably protected variants) as exemplified by the ring substituents listed for compounds of formulae I-IV above, at any position on the aromatic ring. Additionally, the halo leaving group may alternatively be any suitable equivalent, for example, mesylate or tosylate.

Scheme 1Scheme 2

10

An alternate synthetic route is illustrated in General Synthetic Scheme 2 (see above). An R<sup>1</sup>, R<sup>2</sup>-substituted aniline is converted to the corresponding thioisocyanate under standard conditions. This product is then treated with an aniline, where

15

- 24 -

R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup> may be one or more independent substituents (or their suitably protected variants) as exemplified by the ring substituents listed for compounds of formulae I-IV above, at any position on  
5 the aromatic ring and X and Y are as exemplified in the compounds of formulae I-IV, to give the desired substituted amine products.

As can be appreciated by the skilled artisan, the above synthetic schemes are not intended to  
10 comprise a comprehensive list of all means by which the compounds described and claimed in this application may be synthesized. Further methods will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps described above may be  
15 performed in an alternate sequence or order to give the desired compounds.

The compounds of this invention may be modified by appending appropriate functionalities to enhance selective biological properties. Such  
20 modifications are known in the art and include those which increase biological penetration into a given biological compartment (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by  
25 injection, alter metabolism and alter rate of excretion.

The novel compounds of the present invention are ligands for IMPDH. Accordingly, these compounds are capable of targeting and inhibiting IMPDH enzyme.

- 25 -

Inhibition can be measured by various methods, including, for example, IMP dehydrogenase HPLC assays (measuring enzymatic production of XMP and NADH from IMP and NAD) and IMP dehydrogenase spectrophotometric  
5 assays (measuring enzymatic production of NADH from NAD). [See C. Montero et al., Clinica Chimica Acta, 238, pp. 169-178 (1995)].

Pharmaceutical compositions of this invention comprise a compound of formula I or IV or a  
10 pharmaceutically acceptable salt thereof; an additional agent selected from an immunosuppressant, an anticancer agent, an antiviral agent, antiinflammatory agent, antifungal agent, antibiotic, or an antivascular hyperproliferation compound; and any pharmaceutically  
15 acceptable carrier, adjuvant or vehicle. Alternate compositions of this invention comprise a compound of formulae I-IV or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier, adjuvant or vehicle. Such composition may optionally  
20 comprise an additional agent selected from an immunosuppressant, an anticancer agent, an antiviral agent, antiinflammatory agent, antifungal agent, antibiotic, or an antivascular hyperproliferation compound.

25 The term "pharmaceutically acceptable carrier or adjuvant" refers to a carrier or adjuvant that may be administered to a patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof and is nontoxic when

- 26 -

administered in doses sufficient to deliver a therapeutic amount of the compound.

Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as  $\alpha$ -tocopherol polyethyleneglycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tweens or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat. Cyclodextrins such as  $\alpha$ -,  $\beta$ -, and  $\gamma$ -cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl- $\beta$ -cyclodextrins, or other solubilized derivatives may also be advantageously used to enhance delivery of compounds of formulae I-IV.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by

- 27 -

inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. We prefer oral administration or administration by injection. The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending

- 28 -

medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of

5 injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant such as those described in

10 Pharmacopeia Helvetica, Ph. Helv., or a similar alcohol, or carboxymethyl cellulose or similar dispersing agents which are commonly used in the formulation of pharmaceutically acceptable dosage forms such as emulsions and or suspensions. Other commonly

15 used surfactants such as Tweens or Spans and/or other similar emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of

20 formulation.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, emulsions and aqueous suspensions,

25 dispersions and solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents

30 include lactose and dried corn starch. When aqueous

- 29 -

suspensions and/or emulsions are administered orally, the active ingredient may be suspended or dissolved in an oily phase is combined with emulsifying and/or suspending agents. If desired, certain sweetening  
5 and/or flavoring and/or coloring agents may be added.

The pharmaceutical compositions of this invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of  
10 this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa  
15 butter, beeswax and polyethylene glycols.

Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible by topical application. For  
20 application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention  
25 include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream  
30 containing the active compound suspended or dissolved

- 30 -

in a carrier with suitable emulsifying agents. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, 5 benzyl alcohol and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches are also 10 included in this invention.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical 15 formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

20 Dosage levels of between about 0.01 and about 100 mg/kg body weight per day, preferably between about 0.5 and about 75 mg/kg body weight per day of the IMPDH inhibitory compounds described herein are useful in a monotherapy and/or in combination therapy for the 25 prevention and treatment of IMPDH mediated disease. Typically, the pharmaceutical compositions of this invention will be administered from about 1 to about 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic 30 or acute therapy. The amount of active ingredient that



- 31 -

may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 5 95% active compound (w/w). Preferably, such preparations contain from about 20% to about 80% active compound.

When the compositions of this invention comprise a combination of an IMPDH inhibitor of 10 formulae I-IV and one or more additional therapeutic or prophylactic agents, both the IMPDH inhibitor and the additional agent should be present at dosage levels of between about 10 to 100%, and more preferably between about 10 to 80% of the dosage normally administered in 15 a monotherapy regimen. The additional agents may be administered separately, as part of a multiple dose regimen, from the compounds of this invention. Alternatively, those agents may be part of a single dosage form, mixed together with the compounds of this 20 invention in a single composition.

According to one embodiment, the pharmaceutical compositions of this invention comprise an additional immunosuppression agent. Examples of additional immunosuppression agents include, but are 25 not limited to, cyclosporin A, FK506, rapamycin, leflunomide, deoxyspergualin, prednisone, azathioprine, mycophenolate mofetil, OKT3, ATAG, interferon and mizoribine.

According to an alternate embodiment, the 30 pharmaceutical compositions of this invention may

- 32 -

additionally comprise an anticancer agent. Examples of anticancer agents include, but are not limited to, cis-platin, actinomycin D, doxorubicin, vincristine, vinblastine, etoposide, amsacrine, mitoxantrone,  
5 tenipaside, taxol, colchicine, cyclosporin A, phenothiazines, interferon and thioxantheres.

According to another alternate embodiment, the pharmaceutical compositions of this invention may additionally comprise an antiviral agent. Examples of  
10 antiviral agents include, but are not limited to, Cytovene, Ganciclovir, trisodium phosphonoformate, Ribavirin, d4T, ddI, A T, and acyclovir.

According to yet another alternate embodiment, the pharmaceutical compositions of this  
15 invention may additionally comprise an antivasular hyperproliferative agent. Examples of antivasular hyperproliferative agents include, but are not limited to, HMG Co-A reductase inhibitors such as lovastatin, thromboxane A2 synthetase inhibitors, eicosapentanoic  
20 acid, ciprostone, trapidil, ACE inhibitors, low molecular weight heparin, mycophenolic acid, rapamycin and 5-(3'-pyridinylmethyl)benzofuran-2-carboxylate.

Upon improvement of a patient's condition, a maintenance dose of a compound, composition or  
25 combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been  
30 alleviated to the desired level, treatment should

- 33 -

cease. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

As the skilled artisan will appreciate, lower  
5 or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health  
10 status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the infection, the patient's disposition to the infection and the judgment of the treating physician.

In an alternate embodiment, this invention  
15 provides methods of treating or preventing IMPDH mediated disease in a mammal comprising the step of administering to said mammal any of the pharmaceutical compositions and combinations described above. If the pharmaceutical composition only comprises the IMPDH  
20 inhibitor of this invention as the active component, such methods may additionally comprise the step of administering to said mammal an agent selected from an antiinflammatory agent, immunosuppressant, an anticancer agent, an antiviral agent, or an  
25 antivasular hyperproliferation compound. Such additional agent may be administered to the mammal prior to, concurrently with, or following the administration of the IMPDH inhibitor composition.

In a preferred embodiment, these methods are  
30 useful in suppressing an immune response in a mammal.

- 34 -

Such methods are useful in treating or preventing diseases, including, transplant rejection (e.g., kidney, liver, heart, lung, pancreas (islet cells), bone marrow, cornea, small bowel and skin allografts and heart valve xenografts), graft versus host disease, and autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis, juvenile diabetes, asthma, inflammatory bowel disease (Crohn's disease, ulcerative colitus), lupus, diabetes, mellitus myasthenia gravis, psoriasis, dermatitis, eczema, seborrhoea, pulmonary inflammation, eye uveitis, hepatitis, Grave's disease, Hashimoto's thyroiditis, Behcet's or Sjorgen's syndrome (dry eyes/mouth), pernicious or immunohaemolytic anaemia, idiopathic adrenal insufficiency, polyglandular autoimmune syndrome, glomerulonephritis, scleroderma, lichen planus, viteligo (depigmentation of the skin), autoimmune thyroiditis, and alveolitis.

These methods comprise the step of administering to the mammal a composition comprising a compound of any of formulae I-IV and a pharmaceutically acceptable adjuvant. In a preferred embodiment, this particular method comprises the additional step of administering to said mammal a composition comprising an additional immunosuppressant and a pharmaceutically acceptable adjuvant.

Alternatively, this method comprises the step of administering to said mammal a composition comprising a compound of formulae I-IV; an additional immunosuppressive agent and a pharmaceutically acceptable adjuvant.

In an alternate preferred embodiment, these methods are useful for inhibiting viral replication in a mammal. Such methods are useful in treating or

- 35 -

preventing DNA and RNA viral diseases caused by, for example, HTLV-1 and HTLV-2, HIV-1 and HIV-2, nasopharyngeal carcinoma virus, yellow fever, dengue fever, HBV, HCV, HGV, yellow fever virus, dengue fever virus, Japanese encephalitis virus, human papilloma virus, rhinoviruses and Herpes viruses, such as Epstein-Barr, cytomegaloviruses, Herpes Simplex, Types 1 and 2, or Type 6. [See, United States patent 5,380,879].

10               These methods comprise the step of administering to the mammal a composition comprising a compound of any of formulae I-IV, and a pharmaceutically acceptable adjuvant. In a preferred embodiment, this particular method comprises the  
15 additional step of administering to said mammal a composition comprising an additional antiviral agent and a pharmaceutically acceptable adjuvant.

                  Alternatively, this method comprises the step of administering to said mammal a composition  
20 comprising a compound of formulae I-IV; an additional antiviral agent and a pharmaceutically acceptable adjuvant.

                  In another alternate preferred embodiment, these methods are useful for inhibiting vascular  
25 cellular hyperproliferation in a mammal. Such methods are useful in treating or preventing diseases, including, restenosis, stenosis, arteriosclerosis and other hyperproliferative vascular disease.

                  These methods comprise the step of  
30 administering to the mammal a composition comprising a compound of any of formulae I-IV, and a

- 36 -

pharmaceutically acceptable adjuvant. In a preferred embodiment, this particular method comprises the additional step of administering to said mammal a composition comprising an additional antivasular  
5 hyperproliferative agent and a pharmaceutically acceptable adjuvant.

Alternatively, this method comprises the step of administering to said mammal a composition comprising a compound of formulae I-IV; an additional  
10 antivasular hyperproliferative agent and a pharmaceutically acceptable adjuvant.

In another alternate preferred embodiment, these methods are useful for inhibiting tumors and cancer in a mammal. Such methods are useful in  
15 treating or preventing diseases, including, tumors and malignancies, such as lymphoma, leukemia and other forms of cancer.

These methods comprise the step of administering to the mammal a composition comprising a  
20 compound of any of formulae I-IV, and a pharmaceutically acceptable adjuvant. In a preferred embodiment, this particular method comprises the additional step of administering to said mammal a composition comprising an additional antitumor or  
25 anticancer agent and a pharmaceutically acceptable adjuvant.

Alternatively, this method comprises the step of administering to said mammal a composition comprising a compound of formulae I-IV; an additional  
30 antitumor or anticancer agent and a pharmaceutically acceptable adjuvant.

In another alternate preferred embodiment,

- 37 -

these methods are useful for inhibiting inflammation and inflammatory diseases in a mammal. Such methods are useful in treating or preventing diseases, including, osteoarthritis, acute pancreatitis, chronic  
5 pancreatitis, asthma and adult respiratory distress syndrome.

These methods comprise the step of administering to the mammal a composition comprising a compound of any of formulae I-IV, and a  
10 pharmaceutically acceptable adjuvant. In a preferred embodiment, this particular method comprises the additional step of administering to said mammal a composition comprising an antiinflammatory agent and a pharmaceutically acceptable adjuvant.

15 In order that this invention be more fully understood, the following examples are set forth. These examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way.

20

#### General Materials and Methods

All temperatures are recorded in degrees Celsius. Thin layer chromatography (TLC) was carried out using 0.25 mm thick E. Merck silica gel 60 F254  
25 plates and elution with the indicated solvent system. Detection of the compounds was carried out by treating the plate with an appropriate visualizing agent, such as 10% solution of phosphomolybdic acid in ethanol or a 0.1% solution of ninhydrin in ethanol, followed by  
30 heating, and/or by exposure to UV light or iodine

- 38 -

vapors when appropriate. Analytical HPLC was carried out using a Rainin Mycrosorb-MV, 5 $\mu$  Cyano reverse phase column, 3.9mm x 150mm, with a flow rate of 1.0mL/minute and a solvent gradient of 5-100% acetonitrile (0.1%  
5 TFA) in water (0.1% TFA). HPLC retention times were recorded in minutes. NMR spectral data was acquired using a Bruker AMX500 in the indicated solvent.

The IMP dehydrogenase HPLC assay follows our standard conditions for the enzymatic production of XMP  
10 and NADH from IMP and NAD, but utilizes high pressure liquid chromatography on a C18 column with ion pairing reagents to separate all four components. The extent of reaction is then determined from the resulting product peak areas. This assay is particularly useful  
15 for determining the inhibition profiles of compounds which have significant absorbance in the UV-visible region between 290 and 340 nm.

The reaction mixture typically contains 0.1 M KPi; pH 8.0, 0.1M KCl, 0.5 mM EDTA, 2 mM DTT, and 0.2  
20 mM each of IMP and NAD. This solution is incubated at 37°C for 10 minutes. The reaction is started by the addition of enzyme to a final concentration of 20 to 100 nM, and is allowed to proceed for 10 minutes. After the allotted time, the reaction is quenched by  
25 the addition of mycophenolic acid to a final concentration of 0.01 mM.

The extent of conversion is monitored by HPLC using a Rainin Microsorb ODS column C18-200 of dimensions 4.6 X 10 mm and a solvent system containing



- 39 -

tetrabutylammonium sulfate (5mM) in 0.1 M KPi pH 6.0 with a 0-30% methanol gradient over 15 minutes. A similar solvent system has been used previously for the purification of halo-IMP derivatives. [L. C. Antionio and J. C. Wu, Biochemistry, 33, 1753-1759 (1994).] A UV-monitor set at 254 nM is used to detect the four components, and the product peaks are integrated to determine the extent of conversion of the substrates.

For the analysis of inhibitors, the compound in question is dissolved in DMSO to a final concentration of 20 mM and added to the initial assay mixture at the desired concentration in a volume of 2-5% (v/v). The reaction is started by the addition of enzyme and after 10 minutes is quenched as above. After HPLC analysis, the product areas are used to determine the extent of conversion relative to a control assay containing only DMSO and no test compound. IC50 or Ki values are determined from non linear least squares fitting of conversion vs concentration curves to the tight-binding equations of Henderson. [P. J. F. Henderson, Biochem. J., 127, 321 (1972).]

We have measured the inhibition constants of each compound against IMPDH using an adaptation of the method first reported by Magasanik. [B. Magasanik, H. S. Moyed, and L. B. Gehring J. Biol. Chem., 226, p.339 (1957)].

Insofar as compounds of formulae I-IV are able to inhibit IMPDH, they are of evident clinical utility for the treatment of IMPDH mediated disease.

- 40 -

These tests are predictive of the compounds ability to inhibit IMPDH in vivo.

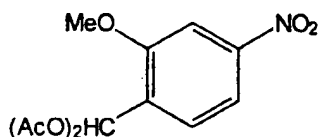
### Experimental Section

#### 5 Synthesis of Representative Examples:

##### Example 1

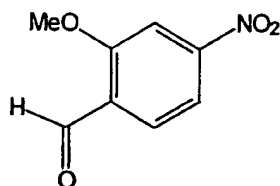
##### Synthesis of Compound 5

10

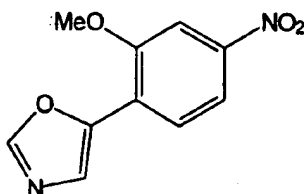
**A1**

To a solution of glacial acetic acid (95mL),  
15 acetic anhydride (95mL, 1mole) and 2-methoxy-4-nitrotoluene (10g, 50mmole) at 0°C was added conc. H<sub>2</sub>SO<sub>4</sub> (14.2mL) in a dropwise fashion. Upon complete addition, CrO<sub>3</sub> (16.67g, 167mmole) was added portion-wise over 120 mins. Following an additional 15 mins of  
20 stirring at 0°C, the reaction mixture was poured over ice and the resulting precipitate was isolated by filtration, rinsing with cold H<sub>2</sub>O. Purification by flash chromatography, eluting with a gradient of 15-50% EtOAc in hexanes, provided 8.14g (51%) A1 as a white  
25 solid. The <sup>1</sup>H NMR was consistent with that of the desired structure.

- 41 -

**A2**

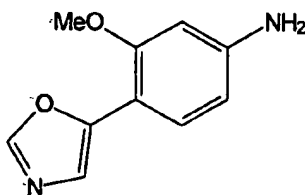
A stirred suspension of **A1** (81.94g, 307mmole) in  
5 dioxane (100mL) was treated with concentrated HCl  
(20mL) and heated at reflux overnight. Upon cooling to  
ambient temperature, the product **A2** precipitated as a  
light yellow crystalline solid in a yield of 40.65g  
(73.1%). The filtrate was concentrated to a volume of  
10 ca. 80mL and a second crop of product crystals was  
driven from solution by the addition of hexanes,  
yielding 8.91g (16.0%). Both batches were identical by  
<sup>1</sup>H NMR and TLC analysis and were consistent with that  
of the desired material. The total yield of **A2** was  
15 49.56g (89.1%).

**A3**

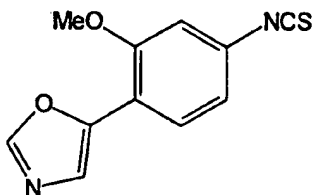
A solution of **A2** (456mg, 2.51mmole), tosylmethyl  
20 isocyanide (490mg, 2.51mmole) and K<sub>2</sub>CO<sub>3</sub> (347mg,  
251mmole) were dissolved in methanol and heated to  
reflux for 1.5 hours. The product mixture was then  
concentrated in vacuo, redissolved in CH<sub>2</sub>Cl<sub>2</sub>, washed

- 42 -

with water and brine, dried over  $\text{Na}_2\text{SO}_4$  and again concentrated in vacuo. Purified product **A3** was obtained through recrystallization ( $\text{Et}_2\text{O}$ /hexanes) to yield 375mg (68%). The  $^1\text{H}$  NMR was consistent with that of the desired structure.

**A4**

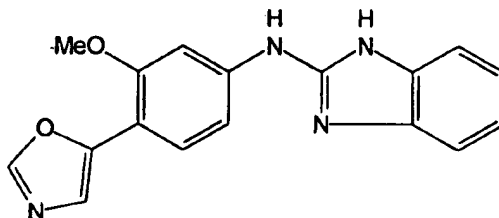
10        A solution of **A3** (4.214g, 19.1mmole) in EtOAc (150mL) was treated with 10%Pd/C (1.05g, 25 wt.% of **A3**) and subjected to 40psi  $\text{H}_2$ (g) (Parr Hydrogenation Apparatus) overnight. The reaction mixture was filtered and concentrated in vacuo. Pure product **A4** 15 was obtained through flash chromatography, eluting with a gradient of 30-40% EtOAc/hexanes, in a yield of 3.4g (93%). The  $^1\text{H}$  NMR was consistent with that of the desired structure.

**A5**

20

- 43 -

A solution of A4 (250mg, 1.3 mmoles) in 10 mL of methylene chloride was treated with 1, 1'-thiocarbonyldi-2(1H)-pyridone (302mg, 1.3 mmoles). The resulting solution was stirred at room temperature for 5 10 min., and then washed once with water and once with 0.5 N HCl. The organic layer was dried with sodium sulfate, filtered, and concentrated *in vacuo*. The resulting oil A5 was used immediately.



10

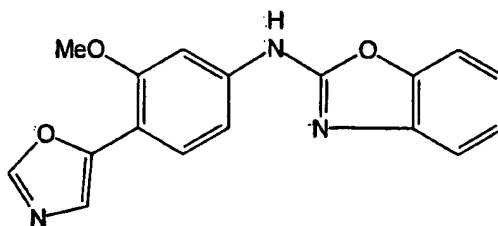
5

Compound A5 (1.3 mmoles) in 44 mL of benzene was treated with phenylene diamine (140mg, 1.3 mmoles). 15 The resulting solution was heated to reflux for 15 min., at which time 405mg (1.95 mmoles) of dicyclohexylcarbodiimide was added. Refluxing was continued for 5 h. After cooling to room temperature a precipitate 5 was isolated by filtration (270 mg, 68% 20 for 2 steps). Mass spectral analysis was consistent with that of the desired structure. <sup>1</sup>H NMR (500MHz, d<sub>6</sub>-DMSO) δ 11 (s, 1H), 9.7 (s, 1H), 8.3 (s, 1H), 7.65 (d, 2H), 7.55 (d, 1H), 7.4 (s, 1H), 7.3 (bd, 2H), 7.0 (bs, 2H), 3.95 (s, 3H).

- 44 -

Example 2

## Synthesis of Compound 8



5

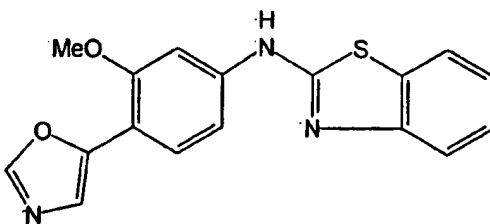
8

A solution of **A4** (500mg, 2.63 mmol) and 2-chlorobenzoxazole (0.2 ml, 1.75 mmol) in DMF (2 mL) was heated to 100 °C and stirred overnight. The reaction mixture was diluted with ethyl acetate and 2N HCl. The layers were partitioned and the organic extracts dried over MgSO<sub>4</sub>. The organics were concentrated in vacuo and the residue purified via medium pressure liquid chromatograph (elution with 1:99 MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give 54 mgs (13%) of **8** as a light yellow solid; TLC: R<sub>f</sub>= 0.20 (3:97 MeOH/CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>HNMR (500 MHz, CDCl<sub>3</sub>) δ 9.2 (bs), 8.0 (s), 7.85 (d), 7.7-7.55 (m), 7.45 (d), 7.35-7.1 (m) 4.15 (s).

- 45 -

Example 3

## Synthesis of Compound 9



5

9

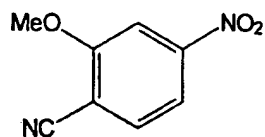
A solution of **A4** (500mg, 2.63 mmol) and 2-chlorobenzothiazole (0.2 ml, 1.5 mmol) in DMF (2 mL) was heated to 100 °C and stirred overnight. The reaction mixture was diluted with ethyl acetate and 2N HCl. The layers were partitioned and the organic extracts dried over MgSO<sub>4</sub>. The organics were concentrated in vacuo and the residue purified via medium pressure liquid chromatograph (elution with 1:99 MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give 176 mgs (41%) of **9** as a light yellow solid; TLC: R<sub>f</sub>= 0.23 (3:97 MeOH/CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>HNMR (500 MHz, CDCl<sub>3</sub>) δ 8.1 (bs), 8.0 (s), 7.85 (d), 7.75 (d), 7.6 (s), 7.5 (s), 7.45 (t), 7.25 (t), 7.15 (d), 4.1 (s).

20

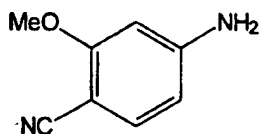
Example 4

## Synthesis of Compound 15

- 46 -

**B1**

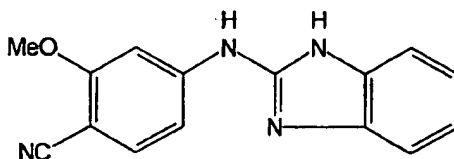
A solution of 2-bromo-5-nitroanisole (1.0g, 4.3mmol) and copper(I)cyanide (388mg, 4.3mmol) in DMF (5mL) was heated to 150°C for four hours. The product mixture was cooled to ambient temperature and poured into water. The resulting precipitate was filtered, dissolved in CH<sub>2</sub>Cl<sub>2</sub>, dried (MgSO<sub>4</sub>) and concentrated to yield a tan solid **B1** in a yield of 634mg (83%). The <sup>1</sup>H NMR was consistent with that of the desired structure.

**B2**

**B1** (192mg, 1.08mmol) and SnCl<sub>2</sub>•2H<sub>2</sub>O (729mg, 3.23mmol) were combined in ethanol (5mL) and heated to 75°C for a period of one hour. The reaction mixture was cooled to ambient temperature, diluted with ethyl acetate, and washed with saturated NaHCO<sub>3</sub> (aq, diluted with 2N NaOH to break emulsion, 2x's) and water (1x). Dried (MgSO<sub>4</sub>) and concentrated to yield an orange solid **B2** in a yield of 140mg (88%). The <sup>1</sup>H NMR was consistent with that of the desired structure.



- 47 -



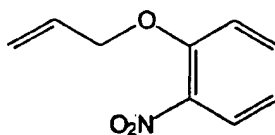
15

Compound 15 was prepared in a fashion analogous to  
5 that of compound 5 wherein B2 (50mg, 0.34mmol) gave  
rise to 15 in a yield of 46.5mg (52%). TLC:  $R_f$  = 0.22  
(60% EtOAc in hexanes).  $^1\text{H}$ NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  11.24  
(s, 1H), 10.12 (s, 1H), 7.68 (s, 1H), 7.61 (d, 1H),  
7.52 (d, 1H), 7.41 (bd, 1H), 7.32 (bd, 1H), 7.05 (m,  
10 2H), 3.92 (s, 3H).

#### Example 5

##### Synthesis of Compound 25

15

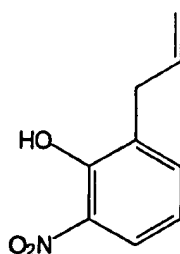


C1

To a solution of 2-nitrophenol (45mmol) in DMF  
20 (10mL) was added powdered  $\text{K}_2\text{CO}_3$  (56mmol) and allyl  
bromide (55mmol). The mixture was stirred at ambient  
temperature for one hour, diluted with ether and washed  
with water (3xs) and brine (1x). The resulting product

- 48 -

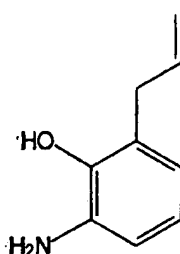
solution was dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated to yield C1 which was utilized with no further purification.



C2

5

C2 (45mmol, neat) was heated overnight at  $180^\circ\text{C}$  under nitrogen. Upon cooling to ambient temperature, the crude product mixture was taken up in ether and extracted with 2N NaOH(aq). This aqueous portion was cooled to  $0^\circ\text{C}$ , acidified (2N HCl) and extracted with ether. The extracts were washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated to yield C2 (15.5mmol). The  $^1\text{H}$  NMR was consistent with that of the desired structure.



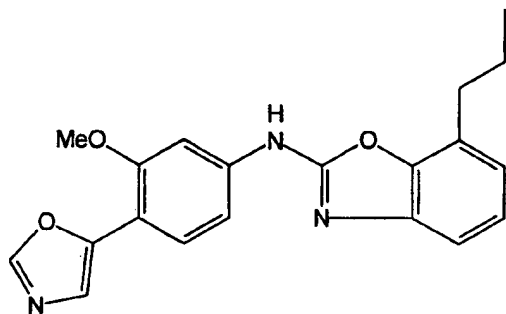
C3

15

C3 (2.2mmol) was dissolved in ethanol and treated with iron (powder, 11mmol) and conc. HCl (1mL) with heating to reflux overnight. The mixture was cooled to

- 49 -

ambient temperature, decanted, basified with  $\text{NaHCO}_3$  (aq) and extracted with ethyl acetate. The extracts were washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated to provide a brown oil. Purification by silica gel chromatography (eluting with 20% ethyl acetate in hexanes) gave C3 in a yield of 248mg, 1.2mmol, 76%) as a dark oil. The  $^1\text{H}$  NMR was consistent with that of the desired structure.



10

25

Compound 25 was prepared in a fashion analogous to that of compound 5 wherein C3 (78mg, 0.526mmol) and A5 (0.53mmol) gave rise to 25 in a yield of 24mg (13%).

TLC:  $R_f$  = 0.28 (3%  $\text{CH}_3\text{OH}$  in  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$ NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.73(br s, 1H), 8.11(s, 1H), 7.89(d, 1H), 7.78(d, 1H), 7.54(dd, 1H), 7.47(s, 1H), 7.34(d, 1H), 7.20(t, 1H), 7.00(d, 1H), 6.08(m, 1H), 5.10(m, 2H), 4.08(s, 3H), 3.60(d, 2H).

20

- 50 -

Example 6

## IMPDH Activity Inhibition Assay

5                   We measured the inhibition constants of the compounds listed in Table II utilizing the following protocol:

                  IMP dehydrogenase activity was assayed following an adaptation of the method first reported by  
10 Magasanik. [Magasanik, B. Moyed, H. S. and Gehring L. B. (1957) J. Biol. Chem. 226, 339]. Enzyme activity was measured spectrophotometrically, by monitoring the increase in absorbance at 340 nm due to the formation of NADH ( $\epsilon_{340}$  is  $6220 \text{ M}^{-1} \text{ cm}^{-1}$ ). The reaction mixture  
15 contained 0.1 M Tris pH 8.0, 0.1 M KCl, 3 mM EDTA, 2 mM DTT, 0.1 M IMP and enzyme (IMPDH human type II) at a concentration of 15 to 50 nM. This solution is incubated at 37°C for 10 minutes. The reaction is started by adding NAD to a final concentration of 0.1M  
20 and the initial rate is measured by following the linear increase in absorbance at 340 nm for 10 minutes. For reading in a standard spectrophotometer (path length 1 cm) the final volume in the cuvette is 1.0 ml. The assay has also been adapted to a 96 well microtiter  
25 plate format; in this case the concentrations of all the reagents remain the same and the final volume is decreased to 200  $\mu\text{l}$ .

                  For the analysis of inhibitors, the compound in question is dissolved in DMSO to a final concentration  
30 of 20 mM and added to the initial assay mixture for preincubation with the enzyme at a final volume of 2-

- 51 -

5% (v/v). The reaction is started by the addition of NAD, and the initial rates measured as above.  $K_i$  determinations are made by measuring the initial velocities in the presence of varying amounts of inhibitor and fitting the data using the tight-binding equations of Henderson (Henderson, P. J. F. (1972) Biochem. J. 127, 321).

These results are shown in Table II.  $K_i$  values are expressed in nM. Category "A" indicates 0.01 to 500 nm activity, category "B" indicates 501-5,000 nm activity, category "C" indicates 5,001 to 15,000 nm activity, category "D" indicates greater than 15,000 nm activity. The designation "ND" is used where a given compound was not tested.

- 52 -

Table II

	Cmpd #	K <sub>i</sub> (nM)
5	1	ND
	2	D
	3	D
	4	D
10	5	B
	6	D
	7	D
	8	A
	9	A
15	10	A
	11	B
	12	A
	13	C
	14	A
20	15	C
	16	A
	17	A
	18	D
	19	D
25	20	D
	21	D
	22	B
	23	B
	24	D
30	25	A

Example 15

35

## Anti-Viral Assays

The antiviral efficacy of compounds may be evaluated in various in vitro and in vivo assays. For example, compounds may be tested in in vitro viral replication assays. In vitro assays may employ whole cells or isolated cellular components. In vivo assays

- 53 -

include animal models for viral diseases. Examples of such animal models include, but are not limited to, rodent models for HBV or HCV, the Woodchuck hepatitis model for HBV, and chimpanzee HCV infection.

5

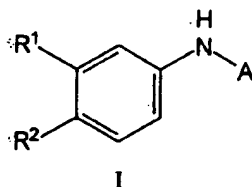
While we have described a number of embodiments of this invention, it is apparent that our basic constructions may be altered to provide other embodiments which utilize the products and methods of  
10 this invention.

- 54 -

CLAIMS

We claim:

1. A method of inhibiting IMPDH activity in  
 5 a mammal comprising the step of administering to said  
 mammal a compound of the formula:



wherein:

- A is a saturated, unsaturated or partially  
 10 saturated monocyclic or bicyclic ring system optionally  
 comprising up to 4 heteroatoms selected from N, O, and  
 S wherein each A optionally comprises up to 4  
 substituents selected from  $R^1$ ,  $R^4$  and  $R^5$ ;

- each  $R^1$  is halogen, CN,  $\text{NO}_2$ ,  $\text{CF}_3$ ,  $\text{OCF}_3$ , OH,  $R^3$ ,  
 15  $\text{OR}^3$ , 1,2-methylenedioxy, 1,2-ethylenedioxy,  $\text{SR}^3$ ,  
 $\text{S(O)R}^3$ ,  $\text{SO}_2\text{R}^3$ ,  $\text{NH}_2$ ,  $\text{NHR}^3$ ,  $\text{N(R}^3)_2$ ,  $\text{NR}^3\text{R}^9$ ,  $\text{COOH}$ , or  
 $\text{COOR}^3$ ;

- each  $R^2$  is independently  $R^1$  or a monocyclic ring  
 system consisting of 5 to 6 members per ring, wherein  
 20 said ring system optionally comprises up to 4  
 heteroatoms selected from N, O, and S, and wherein a  
 $\text{CH}_2$  adjacent to said N, O or S maybe substituted with  
 $\text{C(O)}$ ; and each  $R^2$  optionally comprises up to 2  
 substituents, each substituent independently selected  
 25 from  $R^1$ ;



- 55 -

each  $R^3$  is independently ( $C_1-C_4$ )-straight or branched alkyl, or ( $C_2-C_4$ )-straight or branched alkenyl or alkynyl;

each  $R^4$  is independently ( $C_1-C_6$ )-straight or branched alkyl, or ( $C_2-C_6$ )-straight or branched alkenyl or alkynyl; and each  $R^4$  optionally comprises up to 2 substituents, wherein:

the first of said substituents, if present, is  $R^1$ ,  $R^5$  or  $R^8$ , and

the second of said substituents, if present, is  $R^1$ ;

each  $R^5$  is independently selected from  $OR^6$ ,  $OC(O)R^7$ ,  $OC(O)R^6$ ,  $OC(O)OR^7$ ,  $OC(O)OR^6$ ,  $OC(O)N(R^7)_2$ ,  $OP(O)(OR^7)_2$ ,  $SR^7$ ,  $SR^6$ ,  $S(O)R^7$ ,  $S(O)R^6$ ,  $SO_2R^7$ ,  $SO_2R^6$ ,  $SO_2N(R^7)_2$ ,  $SO_2NR^6R^7$ ,  $SO_3R^7$ ,  $C(O)R^6$ ,  $C(O)OR^6$ ,  $C(O)R^7$ ,  $C(O)OR^7$ ,  $NC(O)C(O)R^7$ ,  $NC(O)C(O)R^6$ ,  $NC(O)C(O)OR^7$ ,  $NC(O)C(O)N(R^7)_2$ ,  $C(O)N(R^7)_2$ ,  $C(O)N(OR^7)R^7$ ,  $C(O)N(OR^7)R^6$ ,  $C(NOR^7)R^7$ ,  $C(NOR^7)R^6$ ,  $N(R^7)_2$ ,  $NR^7C(O)R^6$ ,  $NR^7C(O)R^7$ ,  $NR^6C(O)R^6$ ,  $NR^7C(O)OR^7$ ,  $NR^7C(O)OR^6$ ,  $NR^7C(O)N(R^7)_2$ ,  $NR^7C(O)NR^6R^7$ ,  $NR^7SO_2R^7$ ,  $NR^7SO_2R^6$ ,  $NR^7SO_2N(R^7)_2$ ,  $NR^7SO_2NR^6R^7$ ,  $N(OR^7)R^7$ ,  $N(OR^7)R^6$ ,  $P(O)(OR^7)N(R^7)_2$ , and  $P(O)(OR^7)_2$ ;

$R^6$  is a monocyclic or a bicyclic ring system consisting of 5 to 6 members per ring, wherein said ring system optionally comprises up to 4 heteroatoms

- 56 -

selected from N, O, and S, and wherein a CH<sub>2</sub> adjacent to any of said N, O, or S heteroatoms is optionally substituted with C(O); and each R<sup>6</sup> optionally comprises up to 3 substituents, each substituent independently  
5 selected from R<sup>1</sup>;

each R<sup>7</sup> is independently H, (C<sub>1</sub>-C<sub>4</sub>)-straight or branched alkyl, or (C<sub>2</sub>-C<sub>4</sub>) straight or branched alkenyl; and each R<sup>7</sup> optionally comprises a substituent that is R<sup>8</sup>;

10 R<sup>8</sup> is a monocyclic or a bicyclic ring system consisting of 5 to 6 members per ring, wherein said ring system optionally comprises up to 4 heteroatoms selected from N, O, and S, and wherein a CH<sub>2</sub> adjacent to said N, O or S maybe substituted with C(O); and each  
15 R<sup>8</sup> optionally comprises up to 2 substituents independently chosen from H, (C<sub>1</sub>-C<sub>4</sub>)-straight or branched alkyl, (C<sub>2</sub>-C<sub>4</sub>) straight or branched alkenyl, 1,2-methylenedioxy, 1,2-ethylenedioxy and (CH<sub>2</sub>)<sub>n</sub>-R<sup>1</sup>;

wherein n is 0, 1 or 2;

20 R<sup>9</sup> is an amino protecting group; and

wherein any carbon atom in any R<sup>3</sup>, R<sup>4</sup> or R<sup>7</sup> is optionally replaced by O, S, SO, SO<sub>2</sub>, NH, or N(C<sub>1</sub>-C<sub>4</sub>)-alkyl.

25 2. The method according to claim 1, wherein in said compound, A is a monocyclic aromatic ring system optionally comprising up to 4 heteroatom

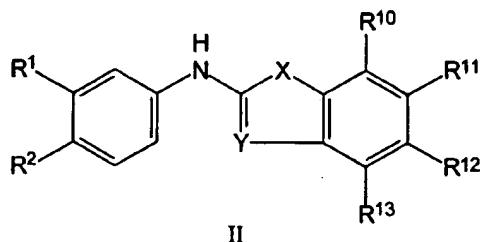
- 57 -

selected from N, O, and S wherein each A optionally comprises up to 4 substituents selected from  $R^1$ ,  $R^4$  and  $R^5$ .

- 5                    3. The method according to claim 1, wherein in said compound, A is a bicyclic aromatic ring system optionally comprising up to 4 heteroatoms selected from N, O, and S, wherein each A optionally comprises up to 4 substituents selected from  $R^1$ ,  $R^4$  and  $R^5$ .

10

4. The method according to claim 1, wherein said compound has the structure of the formula:



15    wherein

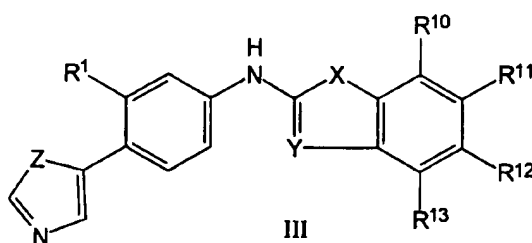
$R^{10}$ ,  $R^{11}$ ,  $R^{12}$  and  $R^{13}$  are each independently selected from  $R^1$  and  $R^4$ , wherein only one of  $R^{10}$ ,  $R^{11}$ ,  $R^{12}$  and  $R^{13}$  may simultaneously be  $R^4$ ; and

X and Y are independently selected from  $CH_2$ ,  $CHR^3$ ,  $CHR^4$ , O, S, NH,  $NR^3$ , and  $NR^4$ .

20

- 58 -

5. A compound of the formula:  
wherein:

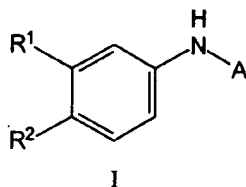


5

$R^1$ ,  $R^{10}$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{13}$ , X and Y are as defined in claim 4 and Z is O, S, NH or  $NR^3$ , wherein  $R^3$  is as defined in claim 1.

10

6. A pharmaceutical composition comprising:  
a. a compound of formula



in an amount effective to inhibit IMPDH activity,  
wherein A,  $R^1$  and  $R^2$  are as defined in claim 1;

15

b. an additional agent selected from an immunosuppressant, an anti-cancer agent, an anti-viral agent, antiinflammatory agent, antifungal agent, antibiotic, or an anti-vascular hyperproliferation agent;

20

c. a pharmaceutically acceptable adjuvant.

- 59 -

7. The composition according to claim 6,  
wherein in said compound, A is a monocyclic aromatic  
ring system optionally comprising up to 4 heteroatom  
selected from N, O, and S wherein each A optionally  
5 comprises up to 4 substituents selected from R<sup>1</sup>, R<sup>4</sup> and  
R<sup>5</sup>.

8. The composition according to claim 6,  
wherein in said compound, A is a bicyclic aromatic ring  
10 system optionally comprising up to 4 heteroatoms  
selected from N, O, and S, wherein each A optionally  
comprises up to 4 substituents selected from R<sup>1</sup>, R<sup>4</sup> and  
R<sup>5</sup>.

15 9. A pharmaceutical composition comprising:  
a. a compound according to claim 5 in  
an amount effective to inhibit IMPDH activity; and  
b. a pharmaceutically acceptable  
adjuvant.

20 10. The pharmaceutical composition according  
to claim 9, additionally comprising an additional agent  
selected from an immunosuppressant, an anti-cancer  
agent, an anti-viral agent, antiinflammatory agent,  
25 antifungal agent, antibiotic, or an anti-vascular  
hyperproliferation agent.

11. A method for treating or preventing  
IMPDH mediated disease in a mammal comprising the step

- 60 -

of administering to said mammal a composition according to claim 6.

12. A method for treating or preventing  
5 IMPDH mediated disease in a mammal comprising the step of administering to said mammal a composition according to claim 9.

13. The method according to claim 12,  
10 wherein said composition additionally comprises an agent selected from an immunosuppressant, an anti-cancer agent, an anti-viral agent, antiinflammatory agent, antifungal agent, antibiotic, or an anti-vascular hyperproliferation agent

15

14. The method according to any one of claims 11 to 13, wherein said method is used to suppress an immune response and wherein said additional agent, if present, is an immunosuppressant.

20

15. The method according to claim 14, wherein said IMPDH mediated disease is an autoimmune disease.

25 16. The method according to any one of claims 11 to 13, wherein the IMPDH mediated disease is a viral disease and wherein said additional agent, if present, is an anti-viral agent.

- 61 -

17. The method according to any one of  
claims 11 to 13, wherein the IMPDH mediated disease is  
a vascular disease and wherein said additional agent,  
if present, is an anti-vascular hyperproliferation  
5 agent.

18. The method according to any one of  
claims 11 to 13, wherein the IMPDH mediated disease is  
cancer and wherein said additional agent, if present,  
10 is an anti-cancer agent.

19. The method according to any one of claims  
11 to 13, wherein the IMPDH mediated disease is an  
inflammatory disease and wherein said additional agent,  
15 if present, is an anti-inflammatory agent.

# INTERNATIONAL SEARCH REPORT

Int. l. Application No

PCT/US 98/04932

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D413/12 A61K31/42 C07D263/58 C07D417/12 C07D235/30

According to International Patent Classification(IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 536 747 A (PATTERSON JOHN W ET AL) 16 July 1996 see column 89-90; claim 1 ---	5-10
A	DE 22 21 866 A (ELY LILLY) 7 December 1972 see page 24-28 ---	5-10
A	GB 1 171 904 A (UNILEVER) 26 November 1969 see page 1 ---	5-10
A	F. MERCHAN ET AL.: "Synthesis of 2-Aryliminoimidazolidines and 2-Arylamino benzimidazoles from Methyl N-Aryldithiocarbamates" SYNTHESIS, vol. 6, 1982, pages 482-484, XP002065887 see table 1 -----	5-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

26 May 1998

Date of mailing of the international search report

09.07.98

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.  
Fax: (+31-70) 340-3016

Authorized officer

Lauro, P



# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 98/04932

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-4, 11-19  
because they relate to subject matter not required to be searched by this Authority, namely:  
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 98/04932

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Although claims 1-4,11-19 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

-----

Claims Nos.: 1-4, 11-19

Although claims 1-4, 11-19 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. l. Application No

PCT/US 98/04932

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5536747 A	16-07-1996	US 5444072 A	22-08-1995
		AU 1917095 A	04-09-1995
		CA 2183533 A	24-08-1995
		CN 1141040 A	22-01-1997
		EP 0745075 A	04-12-1996
		FI 963221 A	16-10-1996
		HR 950071 A	30-06-1997
		JP 9509172 T	16-09-1997
		WO 9522536 A	24-08-1995
DE 2221866 A	07-12-1972	AT 322549 B	26-05-1975
		AU 4179672 A	08-11-1973
		BE 782934 A	03-11-1972
		CA 985286 A	09-03-1976
		DD 102700 A	20-12-1973
		FR 2135296 A	15-12-1972
		GB 1395641 A	29-05-1975
		NL 7206048 A	07-11-1972
		SE 7414459 A	18-11-1974
		US 4088770 A	09-05-1978
		US 4275210 A	23-06-1981
		ZA 7202819 A	19-12-1973
GB 1171904 A	26-11-1969	NONE	